

REMARKS

Claims 1, 6, 7, and 11-13 now stand rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over the combined disclosures of US Patent 5,225,401 to Seymour, US Patent 5,095,110 to Flynn, and US Patent 5,006,344 to Jerzewski.

Applicant's invention utilizes fosinopril sodium in combination with the lubricant zinc stearate having the unexpected result of also effecting tablet degradation. The rate of degradation for each alternative is clearly set out in Applicant's disclosure at column 2 of the published application. It has therefore been clearly determined by the Applicant and established by experimentation that zinc stearate when present as a lubricant in the tablet also had the unexpected advantage of minimizing degradation of fosinopril sodium when compared to the other well known lubricants, such as those listed in the published application, as set out below:

Example No:	1	2	3	4	5
Fosinopril Sodium	10.0	10.0	10.0	10.0	10.0
Lactose Anhydrous	188.0	188.0	188.0	186.0	188.0
Magnesium Stearate	2.0	X	X	X	X
Zinc Stearate	X	2.0	X	X	X
Calcium Stearate	X	X	2.0	X	X
Stearic Acid	X	X	X	4.0	X
Sodium Stearyl Fumarate	X	X	X	X	2.0
	100.0	100.0	100.0	100.0	100.0

[0016] For each of the 5 examples, the ingredients in the proportions listed were mixed together. The powder mixture was then passed through a #40 screen and mixed again. The powder mixture was then compressed into tablets of weight 100 mg each, so that each tablet contained 10 mg of fosinopril sodium.

[0017] Tablets of each of the examples were stored at 60° C. for two weeks and then tested by an HPLC method to determine the degradation products as a percentage of the initial fosinopril sodium content.

[0018] The results were as follows:

Example No.	Lubricant	% Degradation Products
1	Magnesium Stearate	46.2%
2	Zinc Stearate	1.7%
3	Calcium Stearate	75.5%
4	Stearic Acid	2.1%
5	Sodium Stearyl Fumarate	2.8%

[0019] For example 1, using magnesium stearate, the degradation products total 46.2%, whereas for example 5, using sodium stearyl fumarate, the degradation products total only 2.8%. This confirms the teaching of U.S. Pat. No. 5,006,344 that stability is very much improved by using sodium stearyl fumarate as lubricant instead of magnesium stearate.

Referring now to US 5,095,110 granted March 10, 1992 to Flynn, hereinafter referred to as '110, there is taught a process for preparing an olifinated tricyclic lactam which comprises reacting an amine with alkyl nitrite to form a diazoamide compound which is further reacted with strong acid and phosphine, and finally with a strong base in formaldehyde. Clearly this patent teaches a process as set out above and at no point does it discuss fosinopril sodium or an understanding of the differences in the use of various lubricants in pharmaceutical compositions. For example, at column 16, line 15 it is stated that in order to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches that for example talc, stearic acid, or magnesium, calcium or zinc stearate might be used.

~~granulations and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example, talc, stearic acid, or magnesium, calcium, or zinc stearate, dyes, coloring agents, and flavoring~~

Clearly in listing these alternatives they are considered to be equivalents which Applicant has established is clearly not the case. At no time is the issue of degradation rate even raised in '110. The '110 reference therefore teaches that one might be able to use magnesium, calcium or zinc stearate as an acceptable lubricant which establishes a lack of understanding of the differences in the performance of these various lubricants with respect to degradation rates. How might one skilled in the art in reading '110 be motivated or otherwise decide to use any one of the particular lubricants listed in '110 specifically for the purpose of reducing degradation rates when Flynn clearly lacked the understanding of the importance in making a selection, and the resulting differences in degradation rates depending on the selection made.

Referring now to US Patent 5,225,401 issued July 6, 1993, hereinafter referred to as '401, for treatment of congestive heart failure by the administration of a selective inhibitor of neutral endopeptidase and an angiotensin and in one alternative fosinopril sodium. This patent clearly teaches the combination for each specific active but only in combination. The actives may be administered orally or alternatively either in a combined dosage or separately in sequence.

The Examiner in his report refers to some alleged teaching at column 16 of '110. In reviewing the patent at column 16 as set out above it is observed that there is only a general listing of alternative lubricants which would be acceptable namely inter-exchangeable

equivalents. No understanding is present in '401 with respect to the effect on degradation rates resulting from the selection of a lubricant. It is requested that the Examiner reconsider his allegation that in the '110 reference allegedly it would be known to substitute zinc stearate at column 16, lines 16-20 as a substitute for stearic acid described in the '401 reference. Where would the motivation to do so be derived when no understanding of the differences in degradation rates for the alternative lubricants is present in the art? There can be no conclusion reached from the allegations of the Examiner which are clearly lacking in the '401 reference. It is clear that at column 4, line 55 of '401 that both stearic acid and magnesium stearate are listed as alternatives without any appreciation by Seymour that in fact they are not, as set out below:

Illustrative of the adjuvants which may be incorporated in tablets are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate or cellulose; a disintegrating agent such as corn starch, potato starch, alginic acid of the like; a lubricant such as stearic acid or magnesium stearate; a sweetening agent such as sucrose, aspartame,

How would one skilled in the art in reading Seymour differentiate between stearic acid or magnesium stearate absent the understanding of the performance of the former over the latter with respect to rates of degradation. Absent this teaching how might one skilled in the art be motivated to select zinc stearate based on a remote alleged teaching from '110 at column 16, line 15 onward which does not differentiate between stearic acid, magnesium, calcium or zinc stearate. Clearly there is no understanding of the different performances with respect to degradation rates for each alternative. Therefore, how might US Patent 5,006,344, hereinafter referred to as '344, learn from the '401 and the '110 references when they lack direction to one skilled in the art? It is submitted that the '344 reference only teaches the stabilizing of fosinopril with either sodium stearyl fumarate or hydrogenated vegetable oil as a lubricant. Having reached this objective in the '344 there is no need to look any further.

This invention is directed to the discovery that by eliminating magnesium stearate as the lubricant during the tableting of fosinopril sodium and instead employing either sodium stearyl fumarate or hydrogenated vegetable oil, tablets having improved stability are obtained. The tablets thus prepared are significantly less moisture sensitive and have a useful shelf life without the need for protective packaging. Sodium stearyl fumarate is the preferred lubricant since hydrogenated vegetable oil can cause processing problems of sticking to the punch tips during long tableting runs.

EXAMPLE 16

Following the procedure of Example 12 fosinopril sodium tablets were prepared utilizing sodium stearyl fumarate, hydrogenated vegetable oil, and magnesium fumarate as the lubricant. The initial amount of fosinopril sodium was measured and similar measurements were made after 10 days and 25 days storage under varying conditions.

Storage condition	Weight of Fosinopril Sodium		
	Sodium stearyl fumarate formulation	Hydrogenated vegetable oil formulation	Magnesium stearate formulation
Initial	4.99 mg.	4.86 mg.	4.95 mg.
10 days at 75° C. in closed containers	4.36 mg.	4.71 mg.	3.44 mg.
10 days at 50° C., 75% relative humidity in open containers	4.87 mg.	4.60 mg.	3.44 mg.
10 days at 60° C., 75% relative humidity in open containers	4.36 mg.	3.92 mg.	0.90 mg.
25 days at 75° C., in closed containers	4.25 mg.	4.37 mg.	3.39 mg.
25 days at 50° C., 75% relative humidity in open containers	4.69 mg.	4.31 mg.	1.83 mg.

In fact Jerzewski was satisfied with the results achieved and therefore there is no motivation to look elsewhere, and even if there were motivation to look elsewhere, and no admission is made that this is the case, why would '344 look to '110 or '401 who in fact did not appreciate the differences between magnesium, calcium or zinc stearate and therefore no distinction could be reached absent Applicant's teaching. Further no admission is made that there is motivation for '344 to even look to '110 when there is nothing to be gleaned from '110. Further why would '344 look to '401 when in fact there is nothing to be gained from looking to '401 that would be outside of the understanding of a person skilled in the art at that time?

It is therefore submitted that any combination of '344 alone or with '110 and/or '401 will not result in Applicant's improved formulation including the use of zinc stearate as a lubricant with the unexpected advantages expressed in Applicant's disclosure. Zinc stearate is clearly preferred to any of the alternatives, but there is no motivation from '344, '401 or '110 alone

or in combination which could set apart zinc stearate from calcium or magnesium stearate absent the Examiner's attempt at a 20/20 hindsight reconstruction from the art. It is clear from the art that each lubricant must be considered individually and tested individually. Why would '344 suspect that zinc stearate would work any better than calcium stearate or magnesium stearate or in fact better than sodium stearate fumarate?

Applicant submits from a teaching of '344 a man skilled in the art would choose only between hydrogenated oil or sodium stearyl fumarate having dismissed magnesium stearate. The '110 or '401 references do not provide any teaching or motivation to '344 to improve his combination. The Examiner is picking and choosing from the references and improperly isolating the teachings thereof to allege use of zinc stearate without correctly interpreting the citation which does not provide a distinction between calcium stearate, magnesium stearate or zinc stearate. If the knowledge of the differences in the performance of lubricants is so well known as alleged by the Examiner then by process of elimination what would one skilled in the art be motivated to do from the teachings in any of the references alone or in combination? Applicant respectfully submits no more than that which is taught in the references.

Clearly '110 and '401 do not set out a difference in performance of known lubricants listed. Only '344 sets out a difference but only with respect to magnesium stearate. Nothing therefore may be concluded from any combination of '344, '401 and/or '110. The Examiner states "barring a showing of unexpected results, it is the position of the Examiner that this substitution would be determined through routine experimentation". Not so!! The Examiner is referred to the disclosure of Applicant wherein on page 1 of the published application column 2 with respect to paragraph 18 the Applicant has provided a **showing** of unexpected results contrary to the Examiner's allegation and is requested that this allegation be withdrawn as not being based on the facts as presented.

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Zinc Stearate	X	2.0	X	X	X
Calcium Stearate	X	X	2.0	X	X
Stearic Acid	X	X	X	4.0	X
Sodium Stearyl Fumarate	X	X	X	X	2.0
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[0016] For each of the 5 examples, the ingredients in the proportions listed were mixed together. The powder mixture was then passed through a #40 screen and mixed again. The powder mixture was then compressed into tablets of weight 100 mg each, so that each tablet contained 10 mg of fosinopril sodium.

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Applicant has clearly set out the differences with respect to each lubricant which was not understood or addressed in '401 or '110. Only '344 knew of a difference in performance but only with respect to magnesium stearate.

With respect to the Examiner's allegations in relation to the claims which include specific ranges it is submitted that these claims are dependent upon the base claims as is the case for claims 7 and 11 or are combination claims as is the case with claim 12 and some of the newly presented claims. Therefore since in Applicant's view claims 1, 12, 14 and 15 should be allowable for the reasons set out above then, the dependent claims should be allowable as well. Full reconsideration is requested.

With respect to paragraph 8 on page 4 of the Examiner's action respectfully the Examiner has misread the art and has presented a confusing conclusion. It is presumed that what the Examiner meant was that the use of sodium stearyl fumarate taught in '110 would provide some form of alleged motivation to one skilled in the art to replace same with the zinc stearate of '401. In fact this allegation, to read properly, should read to be replaced with the zinc stearate, calcium stearate, or magnesium stearate of '401. '401 did not differentiate between these three alternatives. There is motivation to avoid the magnesium stearate of '344 but not necessarily the calcium stearate also taught in that prior art. One might incorrectly assume this to be the case but then such a conclusion would also apply for other stearic salts like calcium, zinc, or potassium. Therefore what the Examiner considers to be a clear motivation to one skilled in the art is not as clear as the Examiner is alleging. Each case must be evaluated on its own as established in '344 and in Applicant's disclosure.

It is clear from the prior art that none of the inventors Flynn, Seymour, or Jerzewski alone or in combination had an understanding of the advantages of choosing zinc stearate as a lubricant with the minimum of degradation rates for fosinopril sodium, taught and claimed in the present application. This is clearly evidenced by the fact that in the prior art examples they did not appreciate the advantages and benefits of using zinc stearate as a lubricant since in formulating their capsules and tablets they elected to use sodium stearyl fumarate assuming that it would function better than any other known lubricants. It is clear therefore that none of the inventors Flynn, Seymour, or Jerzewski alone or in combination understood the advantages of utilizing zinc stearate as a lubricant in their formulation or were motivated to do so since they did not appreciate the benefits resulting from using zinc stearate over other known lubricants.

Even though Seymour may in fact in his teaching refer to fosinopril sodium he only did so in context of his invention which is a composition including two components, one being the angiotensin II antagonist and the other being the selective inhibitor of endopeptidase. Fosinopril was stated only as one alternative in a list of many possible antihypertensives to be added to the combination. At no time however did Seymour state that he appreciated that the lubricant zinc stearate could also be used to reduce the degradation rates for his composition. There is no discussion of this issue whatsoever in Seymour. Clearly, this being the case he lacks this understanding and teaching now present in Applicant's claims as amended.

US Patent 5,095,110 to Flynn, teaches a process for preparing sulfhydryl containing tricyclic lactams. A review by Applicant of the specification results in the conclusion that fosinopril sodium is not discussed whatsoever in the specification of the '110 reference. The Examiner has stated that it would be obvious to combine the teachings of '110 with the '401 reference. Zinc stearate is not taught in Jerzewski who has formulated his composition with preferably sodium stearyl fumarate or alternatively with hydrogenated vegetable oil in place of magnesium stearate to result in reduced rates of degradation for his composition. Since he has achieved his objective there is no further motivation to improve on his selection. Why would '344 look to '110 and '401? What would be the need or motivation to do so when in fact he doesn't even suggest that further improvements are available?

The traditional test enunciated in Graham vs. John Deere Company 383 U.S. 1, 148 U.S.P.Q. 459 1966, for Section 103 non-obviousness requires the fact finder to make several determinations. The test provides that the scope and content of the prior art be determined, the differences between the prior art and the claims at issue be ascertained, and the level of ordinary skill in the pertinent art be resolved. Thus, the patentability of the claims at hand must stem from the fact that the specific combination of the claimed elements was not disclosed in the prior art and the additional allegation that the specific combination of claimed elements was non-obvious to one of ordinary skill in the art, which Applicant has clearly established as setout above.

Clearly, the prior art does not suggest or provide any reason or motivation to make such a modification as purported by the Examiner. With reference to In Re: Regal, 526 F. 2d 1399, 1403 n. 6, 188 USPQ 136, 139 n. 6 (CCPA 1975).

"There must be some logical reason apparent from positive, concrete evidence of record which justifies a combination of primary and secondary references".

In Re: Geiger, 815 F. 2d 686, 688, 2 USPQ 2d 1276, 1278 (Fed. Cir. 1987) (obviousness can not be established by combining pieces of prior art absent some "teachings, suggestion, or incentive supporting the combination"): In Re: Cho. 813 F. 2d 378, 382, 1 USPQ 2d 1662, 1664 (Fed. Cir. 1987)("discussing the Board's holding that the artisan would have been motivated to combine the references").

Finally,

ATD Corporation v. Lydall, Inc., 48 USPQ 2d 1321, 1329 (Fed. Cir. 1998)

Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. **There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor.**(emphasis added)

In Re: Fritch, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992)

“Wilson and Hendrix fail to suggest any motivation for, or desirability of, the changes espoused by the Examiner and endorsed by the Board. Here, the Examiner relied upon hindsight to arrive at the determination of obviousness. **It is impermissible to use the claimed invention as an instruction manual or “template” to piece together the teachings of the prior art so that the claimed invention is rendered obvious** (emphasis added). The court has previously stated that “[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.”

Therefore, it is Applicant's view that there is no evidence of motivation in the prior art, either within the references themselves, or knowledge generally available to one of ordinary skill in the art, to make the purported changes suggested by the Examiner to arrive at the claimed subject matter, without the Examiner's incorrect use of 20/20 hindsight.

Clearly none of the inventors of the cited references understood the problem solved by Applicant's amended claim 1, that is the use of zinc stearate as a lubricant present also to limit the degradation rate of fosiopril sodium for a tablet.

How then can any combination proposed by the Examiner result in Applicant's invention as set out in his amended claim set, if none appreciated the problem? The motivation in the art is clearly lacking.

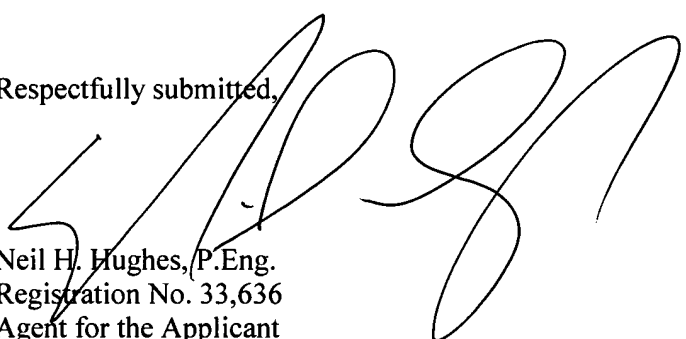
Applicant therefore has assessed the prior art cited by the Examiner and has made amendments to overcome his alleged prior art rejections as well as providing arguments with

regard to the inappropriateness of the Examiner's remarks in misreading the prior art and attempting to create an improper 20/20 hindsight reconstruction. Applicant has also fully refuted the Examiner's combination of the prior art and set out, according to the accepted principles of *Graham v John Deere* cited above, the differences in the claims as amended that distinguish over the prior art cited by the Examiner. There clearly is a lack of motivation in the art, nor is there an expectation of success required by the courts in making any alleged combination of '401, '110 and '344 to create such a combination without creating an improper hindsight reconstruction. Full reconsideration is respectfully requested.

If any other fees should be determined to be required by the Examiner he is requested to access Applicant's Agent's Deposit Account No. 08-3255 for this purpose and advise Applicant's Agent accordingly.

If the Examiner has any questions, he is requested to contact Neil H. Hughes at (905) 771-6414 at his convenience.

Respectfully submitted,



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Encls.